Related substances. Examine by liquid chromatography (*2.2.29*).

Prepare the solutions immediately before use.

Test solution. Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 10.0 mg of *metamizole impurity A CRS* in *methanol R* and dilute to 20.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with *methanol R*.

Reference solution (c). Dissolve 40 mg of *metamizole sodium CRS* in *methanol R* and dilute to 20.0 ml with the same solvent.

Reference solution (d). Take 10 ml of reference solution (c) and boil under a reflux condenser for 10 min. Allow to cool to room temperature and dilute to 20.0 ml with *methanol R*.

Reference solution (e). To 6 ml of reference solution (a) add 1 ml of reference solution (c).

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1.0 ml/min a mixture of 28 volumes of *methanol R* and 72 volumes of a buffer solution prepared by adjusting a mixture of 1000 volumes of a 6.0 g/l solution of *sodium dihydrogen phosphate R* and 1 volume of *triethylamine R* to pH 7.0 with *strong sodium hydroxide solution R*,

– as detector a spectrophotometer set at 254 nm.

When the chromatograms are recorded in the prescribed conditions, the substances elute in the following order: impurity A, metamizole, impurity B, impurity C and impurity D. Inject 10 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is at least 50 per cent of the full scale of the recorder.

Inject 10 µl of reference solution (d). The chromatogram shows two principal peaks due to metamizole and impurity C.

Inject 10 µl of reference solution (e). The test is not valid unless in the chromatogram obtained the resolution between the peaks corresponding to impurity A and metamizole is at least 2.5.

Inject 10 µl of the test solution and 10 µl of reference solution (b) and continue the chromatography for 3.5 times the retention time of metamizole. In the chromatogram obtained with the test solution: the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peaks, apart from the principal peak and the peak due to impurity C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent). The sum of the areas of all the peaks, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with the reference solution (b).

Sulphates (*2.4.13*). Dissolve 0.150 g in *distilled water R* and dilute to 15 ml with the same solvent. The solution complies with the limit test for sulphates (0.1 per cent).

Heavy metals (*2.4.8*). Dissolve 2.0 g in *water R* and dilute to 20 ml with the same solvent. 12 ml of the freshly prepared solution complies with limit test A for heavy metals (20 ppm). Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Loss on drying (*2.2.32*): 4.9 per cent to 5.3 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C.

ASSAY

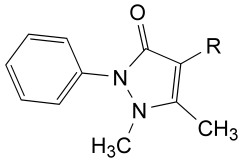
Dissolve 0.200 g in 10 ml of *0.01 M hydrochloric acid* previously cooled in iced water and titrate immediately, dropwise, with *0.05 M iodine*. Before each addition of *0.05 M iodine* dissolve the precipitate by swirling. At the end of the titration add 2 ml of *starch solution R* and titrate until the blue colour of the solution persists for at least 2 min. The temperature of the solution during the titration must not exceed 10 °C.

1 ml of *0.05 M iodine* is equivalent to 16.67 mg of $C_{13}H_{16}N_3NaO_4S$.

STORAGE

Store protected from light.

IMPURITIES



A. R = NHCHO: 4-formylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

B. R = NH_2: 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

C. R = $NHCH_3$: 4-methylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

D. R = $N(CH_3)_2$: 4-dimethylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one.

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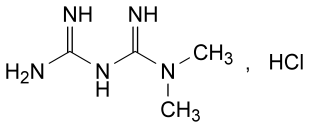
METFORMIN HYDROCHLORIDE

Metformini hydrochloridum



$C_4H_{12}ClN_5$ M_r 165.6

DEFINITION

1,1-Dimethylbiguanide hydrochloride.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white crystals.

Solubility: freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 222 °C to 226 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of *potassium chloride R*.

Comparison: *metformin hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 20 mg of the substance to be examined in *water R* and dilute to 5 ml with the same solvent.

Reference solution. Dissolve 20 mg of *metformin hydrochloride CRS* in *water R* and dilute to 5 ml with the same solvent.

Plate: *TLC silica gel G plate R*.

Mobile phase: upper layer of a mixture of 10 volumes of *glacial acetic acid R*, 40 volumes of *butanol R* and 50 volumes of *water R*.

Application: 5 µl.

Development: over a path of 15 cm.

Drying: at 100-105 °C for 15 min.

Detection: spray with a mixture of equal volumes of a 100 g/l solution of *sodium nitroprusside R*, a 100 g/l solution of *potassium ferricyanide R* and a 100 g/l solution of *sodium hydroxide R*, prepared 20 min before use.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 5 mg in *water R* and dilute to 100 ml with the same solvent. To 2 ml of the solution add 0.25 ml of *strong sodium hydroxide solution R* and 0.10 ml of *α-naphthol solution R*. Mix and allow to stand in iced water for 15 min. Add 0.5 ml of *sodium hypobromite solution R* and mix. A pink colour develops.

E. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *water R* and dilute to 20 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 20.0 mg of *cyanoguanidine R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml to 200.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 20.0 ml with the mobile phase.

Reference solution (c). Dissolve 10.0 mg of *melamine R* in about 90 ml of *water R*. Add 5.0 ml of the test solution and dilute to 100.0 ml with *water R*. Dilute 1.0 ml of this solution to 50.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: irregular, porous silica gel to which benzenesulphonic acid groups have been chemically bonded (10 µm),

or

– *size*: *l* = 0.11 m, Ø = 4.7 mm,

– *stationary phase*: regular, porous silica gel to which benzenesulphonic acid groups have been chemically bonded (5 µm).

Mobile phase: 17 g/l solution of *ammonium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 218 nm.

Injection: 20 µl.

Run time: twice the retention time of metformin hydrochloride.

System suitability: reference solution (c):

– *resolution*: minimum of 10 between the peaks due to melamine and to metformin hydrochloride.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.02 per cent),

– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

12 ml of solution S complies with limit test A. Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 100-105 °C for 5 h.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

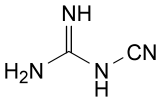
Dissolve 0.100 g in 4 ml of *anhydrous formic acid R*. Add 80 ml of *acetonitrile R*. Carry out the titration immediately. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 16.56 mg of $C_4H_{12}ClN_5$.

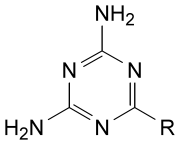
IMPURITIES

Specified impurities: A.

Other detectable impurities: B, C, D, E, F.



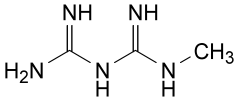
A. cyanoguanidine,



B. R = NH-C(=NH)-NH_2: (4,6-diamino-1,3,5-triazin-2-yl)guanidine,

C. R = $N(CH_3)_2$: *N,N*-dimethyl-1,3,5-triazine-2,4,6-triamine,

D. R = NH_2: 1,3,5-triazine-2,4,6-triamine (melamine),



E. 1-methylbiguanide,

F. CH_3-NH-CH_3: *N*-methylmethanamine.